UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MAY 14 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Du Pont "Ally" Herbicide
Application to Amend Registration and
Petition for Tolerances on Wheat and Barley

TO: Vickie Walters
PM Team Reviewer (23)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 5/13/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 5/6/92
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 5/6/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Du Pont
Chemical: Methyl-2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl] benzoate
Synonym: metsulfuron methyl
Project No.: 2-0665
Caswell No.: 419H
Case No.: 016737/282987
Submission No.: S407569/S407568
DP Barcode: D171710/D171708
Identifying No.: 000352-00435/1F04029
MRID No.: N/A
Action Requested: Add use as a harvest aid; petition to increase tolerances for metsulfuron methyl on wheat and barley to allow for use as a harvest aid.

Comment: The Registrant is applying for an amended registration of "Ally" Herbicide and has submitted a petition for increased tolerances of metsulfuron methyl ("Ally" Herbicide) on wheat (grain and straw) and barley (grain and straw).

Background: "Ally" Herbicide is registered (§ 180.428) for use on barley (grain, green forage, hay, straw), wheat (grain, green

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forage, hay, straw), and grass (fodder, forage, hay).

The toxicology data available to support this request are listed in Table A.

Data Gaps: By current standards, the dermal irritation, dermal sensitization, and mutagenicity (Category III) studies are data requirements for Metsulfuron methyl (see DISCUSSION below).

Tolerance Summary: A Data Residue Evaluation System (DRES) analysis will be performed for the current request for increased residues of Metsulfuron methyl in wheat/barley grain and straw.

Acceptable Daily Intake: The Reference Dose (RfD) for Metsulfuron methyl is 0.25 mg/kg body weight/day, based on the NOEL of 25 mg/kg/day from a 2-year rat feeding study and a 100-fold safety factor.

Effect of Tolerance on ADI: DRES will calculate the effect of this tolerance request on the RfD.

Regulatory Actions Pending: TB II is not aware of any.

DISCUSSION

Two studies (eye and dermal irritation/sensitization) referenced by the Registrant were never submitted to TB II for review. These were obtained by TB II and reviewed for this action; the DER's are appended.

1) Primary dermal irritation (81-5)/sensitization (81-6) - guinea pigs: The test material was determined to be a mild irritant under the conditions of the study. No sensitization was noted. However, without details regarding the conduct of the study, including the size of the test site, exposure duration, justification for not utilizing the technical grade of the test material for the primary irritation test, no definitive statement can be made regarding either primary dermal irritation potential or sensitization of the technical test material.

The study is classified core-Supplementary, pending submission of data/information regarding the conduct of the study, including (1) justification for not utilizing the technical form of the test material and the dose levels utilized; (2) size of the test site; (3) duration of exposure to the test material; (4) whether the test site was covered during the exposure period; (5) whether the test site was washed following exposure; (6) the strain of guinea pig; (7) source of test animals; (6) justification for terminating examination of the test site after 48 hours. This study does not satisfy the guideline requirement (81-5 or 81-6) for either a primary dermal irritation or a dermal sensitization study.
2) Primary eye irritation - rabbits: The test material caused a

moderate area of slight corneal clouding, moderate iritic injection, and severe to moderate conjunctivitis in the treated/unwashed eye. With regard to the washed eye, the same corneal effects and moderate conjunctivitis with no iritic involvement occurred. The unwashed eye was normal within 3 days, and the washed eye within 14 days. The data indicate that the test material may cause severe eye irritation and eye contact should be avoided.

The study is classified Acceptable. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it allows for the selection of the Toxicity Category (I).

The study (MRID # 41773901; listed as 41763901 by Registrant) submitted to fulfill the "Other Genotoxic Effects" category is classified Core Supplementary, pending submission of data/information to support the contention that the limit of solubility was reached for the test materal (see TB II cover memo Taylor to Walters dated 6/6/91, DER dated 5/12/91).

CONCLUSION

TB II has no objection to the request for an amended registration for the new use of Du Pont "Ally" Herbicide as a harvest aid and an increase in tolerances on wheat and barley, provided the RfD is not exceeded as a result of these residue levels. The Registrant should provide assurance that the outstanding data requirements will be satisfied.

DATA AVAILABLE

Metsulfuron methyl

A. Acute oral LD_{50} - rat	LD_{50}> 5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}> 2000 mg/kg Tox.Cat.III
C. Acute inhalation LD_{50} - rat	LC_{50}> 5.3 mg/L/4 hr Tox.Cat.
D. Primary eye irritation - rabbit	Acceptable
E. Primary dermal irritation - GP	no acceptable study
F. Dermal sensitization - guinea pig	no acceptable study
G. 21-Day dermal - rabbit	dermal irritation at 500/2000 mg/kg (6 hr/day) & at 2000 mg/kg after 14-day recovery period; dermal irritation NOEL=125 mg/kg, LEL=500 mg/kg; systemic NOEL=500 mg/kg, LEL=2000 mg/kg, based on diarrhea
H. 90-day feeding - rat	study classified supplementary, but chronic study is available
I. 13-week subchronic - dog	there is a 1-year study
J. Developmental toxicity - rat	maternal NOEL< 40 mg/kg, hyperactivity/ungroomed coat; fetotoxic NOEL>1000 mg/kg; developmental NOEL> 1000 mg/kg
K. Developmental toxicity - rabbit	maternal NOEL= 25 mg/kg, LEL= 100 mg/kg, based on decreased body weight & death; fetotoxic NOEL > 700 mg/kg; developmental NOEL > 700 mg/kg HDT
L. Chronic toxicity - dog	NOEL= 50 ppm, LEL= 500 ppm, based on decreased serum LDH
M. 2-Generation reproduction - rat	systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body-weight gain; reproduct. NOEL > 5000 ppm HDT
N. Chronic tox/carcinogenicity - rat	systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body weight; no increase in tumors
O. Carcinogenicity - mouse	systemic NOEL= 500 ppm, LEL= 5000 ppm, based on decreased body weight; no increase in tumors
P. Mutagenicity - Category I	Ames assay - negative
Category II	Chrom. aber. CHO positive ± activation; rat bone marrow aber./mouse micronucleus - negative
Category III	no acceptable study

Q. Metabolism - rat	rapid elimination, mostly in urine, largely unchanged

Metsulfuron methyl (60%) - DPX (ALLY)

A. Acute oral LD_{50} - rat	LD_{50}> 5000 mg/kg Tox.Cat.IV
B. Acute dermal LD_{50} -rabbit	LD_{50}> 2000 mg/kg Tox.Cat.III
C. Primary eye irritation - rabbit	corneal opacity in one eye at 24 hrs.; cleared in 48 hrs. Tox. Cat.III
D. Primary dermal irritation - rabbit	slightly irritating; Tox.Cat. IV
E. Dermal sensitization - guinea pig	no sensitization

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Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 5/7/92
Section II Head, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation/sensitization (81-5,6)-guinea pigs

CASWELL NUMBER: 419H

MRID NUMBER: 403578-02

TEST MATERIAL: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino-carbonyl]aminosulfonyl]-methyl ester

SYNONYMS: IN T6316; metsulfuron methyl; "ALLY"

STUDY NUMBER: HLR 797-80

SPONSOR: DuPont

TESTING FACILITY: Haskell Laboratory for Toxicology & Industrial Medicine

TITLE OF REPORT: Primary Skin Irritation and Sensitization Test on Guinea Pigs

AUTHOR(S): Polly Ashley

REPORT ISSUED: October 9, 1980

CONCLUSION: The test material was determined to be a mild irritant under the conditions of the study. No sensitization was noted. However, without details regarding the conduct of the study, including the size of the test site, exposure duration, justification for not utilizing the neat test material for the primary irritation test, no definitive statement can be made regarding either primary dermal irritation potential or sensitization of the technical test material.

Quality Assurance: There was no quality assurance statement, but a statement of compliance with FIFRA Good Laboratory Practice Standards was provided.

TOXICITY CATEGORY - not determined.

CLASSIFICATION: Core-Supplementary. This study does not satisfy the guideline requirement (81-5 or 81-6) for either a primary dermal irritation or a dermal sensitization study. This study needs to be repeated as two separate studies; i.e., a primary dermal irritation study and a dermal sensitization study are data requirements.

I. MATERIALS

1. Test compound: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino-carbonyl]aminosulfonyl]-methyl ester; Description: none provided; Batch #: 13,608, INT-6316-11, N.B. 8415-13; Purity: ≈100%.

2. Test animals: Species: Albino guinea pigs; Strain: not stated; Age: not stated; Weight: 435-439 grams; Source: not stated.

II. METHODS

A. General: Prior to initiation of the study, a range-finding study was performed on 3 male guinea pigs to test for skin irritation potential. It was found that the test material was a skin irritant as low as 50% (w/w) in dimethyl phthalate, but not at 40%.

Ten unexposed guinea pigs were used in the primary irritation test. The test material was applied to the shaved, intact shoulder skin (test site size not provided) and rubbed lightly (0.05 mL of either a 40% or a 4% suspension of test material in dimethyl phthalate). The induction phase for sensitization was a series of 4 sacral intradermal injections of 0.01 mL of a 1.0% solution of dimethyl phthalate, one each week beginning 2 days after the test for primary irritation. After a 2-week rest period, the test animals were challenged for sensitization by applying and lightly rubbing in 0.05 mL of a 40% or 4% suspension as before on shaved, intact shoulder skin. Concurrently, 10 unexposed guinea pigs (controls) of the same age were administered identical topical applications. NOTE: There were few details provided; no mention was made of what feed was provided or whether feed and water were available ad libitum throughout the study; no indication of whether both sexes were used; no information on when the skin was shaved or the size of the area exposed or how long the test material was in contact with the skin; no information on how the test material was held in place or what procedures were used to prevent ingestion of the test material by the animals, or whether the test sites were washed following exposure. The results suggest that test sites were examined at 24 and 48 hours in both the primary irritation and challenge tests; it cannot be determined if these times are after test material removal or after study initiation.

With regard to how the test sites were evaluated, a Reaction Code (primary irritation) was given as: +, ++, +++ = mild, moderate, strong erythema; ++++ = erythema plus edema; +++++ = necrosis. The Sensitization Response Code was given as: sensitization is defined as a significant score increase at challenge over the response expected from

the same amount applied initially or on the concurrent controls.

III. RESULTS

Only summary data were provided. Benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazim-2-yl)aminocarbonyl]aminosulfonyl]-methyl ester caused mild erythema in 24 and 48 hours when tested as a 40% suspension in dimethyl phthalate;no reaction was observed at 4%. No sensitization response was observed at either dose level.

Reactions on Intact Guinea Pig Skin♦

Group	Test Animals		Control Animals	
Concentration in dimethyl phthalate	40%	4%	40%	4%
Primary Irritation				
24 hours	2+/8-	10-		
48 hours	1+/9-	10-		
Challenge				
24 hours	2+/8-	10-	1+/9-	10-
48 hours	1+/9-	10-	1+/9-	10-

♦ +, ++, +++ = mild, moderate, strong erythema; ++++ = erythema plus edema; +++++ = necrosis; - = negative

IV. CONCLUSIONS

The test material was determined to be a mild irritant under the conditions of the study. No sensitization was noted. However, without details regarding the conduct of the study, including the size of the test site, exposure duration, justification for not utilizing the neat test material for the primary irritation test, no definitive statement can be made regarding either primary dermal irritation potential or sensitization of the technical test material.

Toxicity Category - cannot be determined without additional data.

V. CLASSIFICATION: Core-Supplementary. This study does not satisfy the guideline requirement (81-5/81-6) for either a primary dermal irritation or a dermal sensitization study. It is to be noted that, in addition to the deficiencies listed below, it is not acceptable to combine these two studies into one study. Both a primary dermal irritation study and a dermal sensitization study are data requirements for DuPont "Ally" herbicide.

VI. STUDY DEFICIENCIES

There are numerous deficiencies in this study report, mainly due to the lack of detail. There are no individual data on the animals or how they were housed, their strain, source, individual daily observations of the test animals, etc.. Other deficiencies include (1) the lack of a justification for not utilizing the technical form of the test material in the primary dermal irritation study or the dose levels utilized; (2) no mention of the size of the test site; (3) the duration of exposure to the test material was not stated; (4) no information on whether the test site was covered during exposure or washed following exposure; and (5) no justification for terminating test site examination after 48 hours.

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Reviewed by: Linda L. Taylor, Ph.D. Linda Taylor C 4/30/92
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Secondary Reviewer: K. Clark Swentzel K Clark Swentzel 5/1/92
Section II Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation-rabbits (81-4)

CASWELL NUMBER: 419H

MRID NUMBER: 403578-01

TEST MATERIAL: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino-carbonyl]aminosulfonyl]-methyl ester

SYNONYMS: IN T6316; metsulfuron methyl; "ALLY"

STUDY NUMBER: HLR 717-80

SPONSOR: DuPont

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: IN T6316 Eye Irritation Test in Rabbits

AUTHOR(S): LS Silber

REPORT ISSUED: October 13, 1980

CONCLUSION: The test material caused a moderate area of slight corneal clouding, moderate iritic injection, and severe to moderate conjunctivitis in the treated/unwashed eye. With regard to the washed eye, the same corneal effects and moderate conjunctivitis with no iritic involvement occurred. The unwashed eye was normal within 3 days, and the washed eye within 14 days. The data indicate that the test material may cause severe eye irritation and eye contact should be avoided.

TOXICITY CATEGORY - I

CLASSIFICATION: Acceptable. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it allows for the selection of the Toxicity Category.

I. MATERIALS

1. Test compound: benzoic acid, 2-[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]aminosulfonyl]-methyl ester; Description: none provided; Batch #: 13,531, INT-6376-5, N.B. 7933-156; Purity: ≈95%.

2. Test animals: Species: rabbits; Strain: New Zealand white; Age: not stated; Weight: not stated; Source: B&H Rabbitry, Wm. Frye, Rockville, MD.

II. METHODS

Two male rabbits were utilized for the study. Ten milligrams of the test material (as received) was placed into the conjunctival sac of the right eye of each rabbit. NOTE: No statement was made that the left eye of each rabbit served as a control or that it was even examined. After 20 seconds, 1 treated eye was washed with tap water for 1 minute; the other treated eye was not washed. Observations of the cornea, iris, and conjunctiva were made with an ophthalmoscope at 1 and 4 hours, and at 1, 2, 3, 6, and 14 days. Fluor-i-strip® stain and a slit lamp biomicroscope were used at examinations after the day of treatment.

III. RESULTS

The results are listed in the table below.

Treatment	Cornea	Iris	Conjunctiva
Unwashed (10 mg)	small area of slight clouding at 1 hr & 1 day; moderate area of slight clouding at 4 hrs & 1 day	moderate injection day 1	redness: moderate 1 hr-1 day; swelling: moderate 1 hr-1 day; slight at day 2 discharge: copious at 1 hr; moderate at 4 hrs-1 day; mild at day 2; Hemastix® + 1 hr-2 days
Washed (10 mg)	moderate area of slight clouding 1-4 hrs, decreasing to a local area 2-6 days	no involvement	redness: moderate 1-4 hrs swelling: mild 1-4 hrs discharge: moderate 1 hr & 1 day; copious at 4 hrs; Hemastix® + 1-4 hrs

The author stated that the test material caused a moderate area of slight corneal clouding, moderate iritic injection, and severe to moderate conjunctivitis in the treated eye. With regard to the washed eye, it was concluded that the same corneal effects and moderate conjunctivitis with no iritic involvement occurred. The unwashed eye was normal within 3 days, and the washed eye within 14 days. The author concluded that the test material may cause severe eye irritation and eye contact should be avoided. It is to be noted that washing of the one treated eye occurred after 20 seconds; the criteria state that the eye should not be washed for at least 24

hours. Additionally, there was no examination of the eyes reported prior to treatment.

A quality assurance statement and a statement of compliance with FIFRA Good Laboratory Practice Standards were signed and dated.

IV. CONCLUSIONS

The test material caused a moderate area of slight corneal clouding, moderate iritic injection, and severe to moderate conjunctivitis in the treated/unwashed eye. With regard to the washed eye, the same corneal effects and moderate conjunctivitis with no iritic involvement occurred. The unwashed eye was normal within 3 days, and the washed eye within 14 days. The data indicate that the test material may cause severe eye irritation and eye contact should be avoided. Although this study does not meet the criteria for a primary eye irritation study in rabbits, it allows for the selection of a Toxicity Category (I), and it is acceptable.

Toxicity Category - I, since exposure to the test material was for 20 seconds only before washing occurred and, although the effects observed had cleared by day 14, a longer exposure (at least 24 hours) may have caused more damage and/or persistence of the effects. Additionally, since only 2 animals were used, this was not an adequate test to determine persistence of the effects.

V. CLASSIFICATION: Acceptable

This study does <u>not</u> satisfy the guideline requirements (§81-4) for a primary eye irritation study in rabbits, but it is adequate for setting the Toxicity Category for primary eye irritation.

VI. STUDY DEFICIENCIES

There are several deficiencies in the study report/study. No information was provided regarding (1) quarantine of the rabbits prior to study initiation; (2) identity of food provided or whether food and water were available <u>ad libitum</u> throughout the study; (3) whether the eyes of each rabbit were examined prior to treatment; (4) body weights or clinical signs. Additionally, the one eye that was washed after treatment was washed after only 20 seconds of contact with the test material (contact for at least 24 hours is recommended).

Tox Chem No. 419H Metsulfuron methyl File Last Updated _____ Current Date 5/7/92

STUDY/LAB/STUDY #/DATE	MATERIAL	EPA MRID NO.	RESULTS: LD50, LC50, PIS, NOEL, LEL	TOX CATEGORY	CORE GRADE/DOC. #
Primary dermal irrit. Species: guinea pig MLR 797-80; Haskell Lab. Tox. & Ind. Med; 10/9/80	Metsulfuron methyl (100%)	403578-02	The test material was determined to be a mild irritant under the conditions of the study. No sensitization was noted. However, without details regarding the conduct of the study, including the size of the test site, exposure duration, justification for not utilizing the neat test material for the primary irritation test, no definitive statement can be made regarding either primary dermal irritation potential or sensitization of the technical test material. This study does not satisfy the guideline requirement (81-5 or 81-6) for either a primary dermal irritation or a dermal sensitization study. This study needs to be repeated as two separate studies; i.e., a primary dermal irritation study and a dermal sensitization study.		Supplementary
Primary eye irritation Species: rabbit MLR 717-80; Haskell Lab. Tox. & Ind. Med.; 10/13/80	Metsulfuron methyl (=95%)	403578-01	The test material caused a moderate area of slight corneal clouding, moderate iritis injection, and severe to moderate conjunctivitis in the treated/unwashed eye. With regard to the washed eye, the same corneal effects and moderate conjunctivitis with no iritis involvement occurred. The unwashed eye was normal within 3 days, and the washed eye within 14 days. The data indicate that the test material may cause severe eye irritation and eye contact should be avoided. This study does not satisfy the guideline requirement (81-4) for a primary eye irritation study in rabbits, but it allows for the selection of the Toxicity Category.	I	Acceptable

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